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COMMENT

Controlled obesity status: a rarely used concept, but with particular importance in the COVID-19 pandemic and beyond

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Abstract
Obesity is a chronic disease that causes and aggravates several other diseases, and early reports suggest it is an important risk factor for COVID-19 severity. Although a deeper understanding of this relationship is vital, it is also important to inform the general public about the risks and, ideally, offer strategies to mitigate the risks. As "resolution" of obesity in the short-term is not feasible, it is indeed possible that smaller weight losses and increase in physical activity can actually reduce the risks. In this context, we propose that a term called "controlled obesity" be more often used and studied, in which those who have lost over 10% of their maximal weight and, ideally, are physically active are considered healthier. This context can have much broader usefulness, beyond the pandemics, as evidence points that weight loss over 10% can significant reduce overall health risks, irrespective of final BMI.

Introduction

Obesity is a chronic and recurrent disease associated with increased disability, comorbidities, and reduced quality of life, as well as life expectancy. Several severe diseases are caused or aggravated by obesity and early reports on Covid-19 infection have included obesity as an important risk factor for disease severity [1–5]. Recently, the Centers for Disease Control and Prevention included body mass index (BMI) over 30 kg/m^2 as a risk factor.

Reporting obesity as a disease associated with Covid-19 severity is utterly important for clinical care, research and public health. However, there have been reports of increased stigma and personal responsibility, as obesity has been seen as a lifestyle choice. It is clearly important to provide a right message in which there is no blame the individual, but, at the same time, emphasize strategies to mitigate the risks. If obesity is a disease, achieving a "normal weight" would be the only way to mitigate the risks or is it possible to have a "controlled obesity state", in which risks of several diseases are reduced?

For example, as a comparison, diabetes is also a risk factor for Covid-19 and several epidemiological studies have shown that good glycemic control is associated with reduced risk of infection. So, a simple public message for diabetes is to maintain your blood sugar under control (generally an HbA1c < 7%), but not necessarily in a non-diabetic level. Shouldn't we do the same with obesity?

Obesity as an important risk factor for COVID-19 severity

Obesity has consistently been associated with increased COVID-19 severity, hospitalization rates and mortality, although the magnitude of the relation is still unclear as data are heterogeneous, due to different study protocols and populations [1–6].

The very large database of OpenSAFELY study examined more than 10,000 deaths in the UK and compared to over 17 million people from the UK Biobank. In this study, obesity was divided according to BMI: 30–34.9, 35–39.9 and over 40 kg/m^2 or more, and these ranges were associated with a 1.23, 1.81 and 2.66 increased in risk of death [3]. Other studies found higher rates of hospitalization and mechanical ventilation in individuals with obesity [2, 5], and

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one meta-analysis found a 2.31 increased risk of COVID-19 complications in those with obesity diagnosis [3]. Moreover, the impact of the disease seems to be even greater in younger populations, which led to some authors to propose that "obesity shift severe COVID-19 to younger ages" [6].

The mechanisms by which obesity is associated with severe COVID-19 are still unknown, but several have been proposed [1, 2, 5]: increased inflammation, with enhanced production of cytokines; increased risk of microthrombosis; respiratory dysfunction (as decreased pulmonary expandability and cardiorespiratory fitness); technical difficulties in intensive care units (challenging orotracheal intubation and eight limits in imaging exams, less benefits of prone position); more prolonged viral shedding; and increased risk of other comorbidities associated with worse prognosis (as type 2 diabetes, hypertension, sleep apnea and cardiovascular disease). Likely, many of those factors are closely linked to insulin resistance and visceral fat and improving insulin sensitivity could hypothetically reduce risks [1, 7].

Obesity, weight loss and hard outcomes in observational data and RCTs

Unfortunately, we have very little evidence that voluntary clinical weight loss is associated with reduced hard outcomes, even on observational data, due to several reasons.

In the first place, clinical meaningful and sustained weight loss is very hard to be achieved, even in dedicated clinical trials. Even studies in which intensive behavior treatment was offered have shown no more than 10% of individuals achieving 10% weight loss after 1 or 2 years [8, 9].

Schwartz and colleagues brilliantly reviewed the biological, and not psychological reasons why weight loss and maintenance is so hard to achieve [9]. Briefly, probably a hypothalamic set-point exists in which every effort for losing weight is counterbalanced by increased hunger and drive to eat, reduced satiety and decreased energy expenditure.

In this context, in epidemiological data, probably the vast majority of patients with clinical meaningful weight loss represent a group of involuntary weight loss, due to a underlying disease. So, only data from intervention studies that produces clinical meaningful mean weight losses can clearly demonstrates the benefits of weight loss.

The best evidence of reduced outcomes after weight loss comes from bariatric surgery cohorts. The SOS Study, for example, has shown reduced risk of mortality, cardiovascular events, cancer (mostly in women) and several other diseases, as type 2 diabetes and sleep apnea [10]. Data about infection rate, however, are virtually non-existent.

Surely, we cannot exclude that the benefits come from the surgical procedure itself, but as the majority of patients in SOS performed restrictive procedures, it is very unlikely that the benefits are weight loss independent [11]. Several other surgical cohorts have shown similar results and bariatric surgery is the most effective and evidence-based long-term treatment for severe obesity.

In contrast, however, the evidence regarding non-surgical weight loss on reduced hard outcomes, including cardiovascular events and mortality are less compelling. An example of failure is the LOOK AHEAD Study in which intensive behavior treatment was not superior to a control group regarding cardiovascular events after 9 years in a type 2 diabetes population [8]. However, a sub-analysis focusing in those who attained at least 10% weight loss, indeed evidenced a reduction of cardiovascular events [12]. A meta-analysis of RCTs with more than 17,000 confirmed that intentional weight loss was associated with a 15% reduction in all-cause mortality [13].

In regard to infections, though, there are not any data from weight loss intervention studies. Nevertheless, the same is true for diabetes: there is no direct evidence from intervention trials that glycemic control reduces infections, although there is high biological plausibility.

Clinical achievable weight loss and risk factors

Since weight loss to "normalize" BMI is rarely achieved, there is good evidence that clinical achievable weight loss improves cardiovascular risk factors and several substitutive markers [14]. For example, 5–7% weight loss leads to a reduction in in insulin resistance and consequently, reduction in glycemia, triglycerides, blood pressure and ectopic fat deposition, as liver fat [14]. 10% weight loss has a dramatic effect on liver fibrosis in patients with non-alcoholic liver disease, and several other risk markers.

If visceral fat and insulin resistance are important players in the relationship of body fat and COVID-19 severity [1, 7], modest weight losses could have impact on reduction of risks, as already suggested [1], although no direct evidence exists. Low-grade inflammation reduces as well after weight loss. Magkos et al. have shown that 11–16% weight loss can substantially reduce obesity-related inflammation [15]. The same is true about pulmonary function and sleep apnea severity, other possible mediators of the relationship of obesity with COVID-19 severity [14].

An important concept here is that these risk reductions are observed irrespective of baseline BMIs. In this regard, similar percentage weight losses in individuals with very similar basal BMIs can have similar benefits. Why this happens is not exactly known, but is probably related to ectopic lipid deposition and personal fat thresholds, in which insulin resistance and metabolic disturbances appears when the subcutaneous expansion limit is achieved [1]. Continuous

weight gain will lead to ectopic fat deposition in organs like liver, muscle and pancreas and increased insulin resistance can also act as a curb to further weight gain.

Controlled obesity status: would it be an important clinical message?

Shouldn´t we use more often the term "controlled obesity" for those individuals, not only for Covid-19, but generally speaking, to nearly all diseases associated to obesity? Surely, direct evidence is still scarce, as we pointed out, but this can be a simple message, especially in situations as Covid-19 pandemics, in which is virtually impossible to lose a massive amount of weight in a short period of time.

The concept of a metabolically healthy obesity, achieved through moderate weight reductions not enough to reach the BMI of 25 kg/m^2 target, is not novel and has been previously proposed as the "low hanging fruit" in obesity treatment [16].

The main problem in using this concept is that there is no universal number below which the risk is reduced, since it depends on the individual weight history, which is also subject to recall bias. Other factor that could bias this analysis is the already discussed reverse causation: weight loss could be a proxy of a subclinical disease, in which the overall prognosis would be poor. So, ideally, we should exclude data on those who unintentionally lost weight in the past.

Nonetheless, we believe that attaining self-reported maximal weight would be a relevant clinical information to be considered in future studies with Covid-19 and beyond [17]. If we demonstrate, even with case–control studies, that those who voluntarily lost weight in the past have a better prognosis in Covid-19, we can start providing a simple and achievable message for those with obesity. Data of disease severity on patients who performed bariatric surgery could likewise be useful.

If, hopefully, the pandemic vanishes in the future as a vaccine is delivered, we could still use this concept to improve metabolic health and reduce the stigma of individuals with obesity, in which bariatric surgery is not indicated or feasible.

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Compliance with ethical standards

Conflict of interests BH received travel grants from Novo Nordisk and Aché Pharmaceuticals; received honoraria for lectures from Novo Nordisk, Eli Lilly, and Boehringer-Ingelheim; and is on the Advisory Board for Novo Nordisk and Eli Lilly. MCM received travel grants from Novo Nordisk; received honoraria for lectures from Novo Nordisk, EMS Pharmaceutical, and Eurofarma Pharmaceuticals; and is on the Advisory Board for Novo Nordisk.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No Informed Consent.

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